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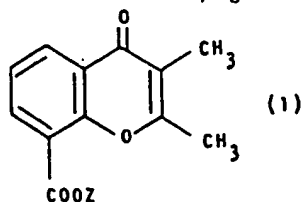
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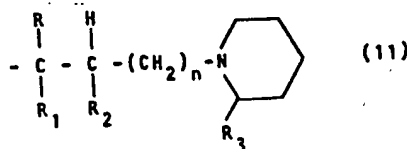
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(54) 3-Methylflavone-8-carboxylic acid esters.

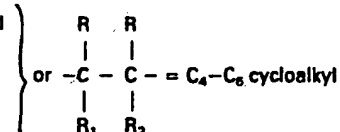
(57) 3-Methylflavone-8-carboxylic acid esters I are provided. They may be prepared by condensing a 3-methylflavone-8-carboxylic acid halide (preferably the chloride with an aminoalcohol ZOH. Condensation conditions are (a) no solvent, 140-200°C, excess flavone derivative or (b) organic solvent, 0°C to reflux, equimolar reactant proportions, hydrogen halide acceptor optional. The esters have muscle relaxant and calcium blocking action. They are also anaesthetics and anti-inflammatory agents.



Z = N-methylpiperidyl, trotyl, quinuclidyl or



n = 0,1

R = H, Ph, C<sub>1</sub>-C<sub>4</sub> alkylR<sub>1</sub> = H, C<sub>1</sub>-C<sub>4</sub> alkylR<sub>2</sub> = H, OHR<sub>3</sub> = H, C<sub>1</sub>-C<sub>4</sub> alkyl

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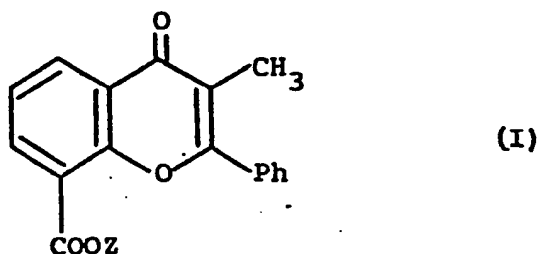
TITLE:

3-Methylflavone-8-carboxylic acid esters

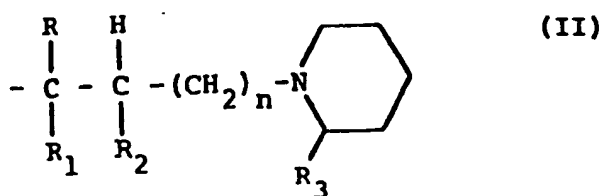
DESCRIPTION:

The invention relates to esters of 3-methylflavone-8-  
 5 -carboxylic acid, to pharmaceutically acceptable salts  
 thereof, to processes for the preparation of the esters  
 and their salts, and to pharmaceutical compositions  
 containing the esters or their salts. It is known that  
 certain esters of 3-methylflavone-8-carboxylic acid  
 10 exhibit a good spasmolytic activity (see United States  
 Patent Specification No. 2,921,070). Their action,  
 however, might be improved by increasing their stability  
 at physiological pH.

The invention provides 3-methylflavone-8-carboxylic acid  
 15 esters having the general formula I



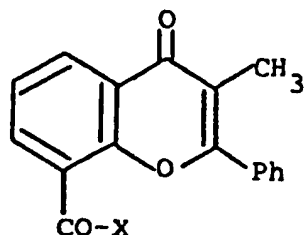
wherein Z represents an N-methylpiperidyl, troyl or  
 quinuclidyl group or a group of the general formula II



in which n is 0 or 1, R represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms or a phenyl group,  $R_1$  represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms,  $R_2$  represents a hydrogen atom or a hydroxy group, or R,  $R_1$  and  $R_2$  together with the carbon atoms to which they are attached represent a cycloalkyl ring having from 4 to 6 carbon atoms, and  $R_3$  represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, and further provides pharmaceutically acceptable salts of such esters.

The compounds according to the invention have been found to exhibit powerful smooth muscle relaxant, calcium blocking, local anaesthetic, and anti-inflammatory properties. They are considerably stable at the physiological pH, so that the half-life of the drug is highly prolonged. It has been found moreover, that the novel esters possess further activities whereas their toxicity is diminished or, at most, unaltered when compared with the known compounds.

The invention further provides a process for the preparation of the compounds having the general formula I as above defined, the process comprising condensing a 3-methylflavone-8-carboxylic acid halide having the general formula III



(III)

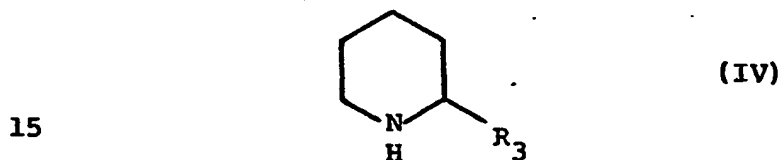
5        wherein X represents a halogen atom with an aminoalcohol  
of the general formula ZOH, wherein Z is as above defined.

The 3-methylflavone-8-carboxylic acid halide is preferably  
3-methylflavone-8-carboxylic acid chloride (III, X=Cl),  
and is a known compound (see United States Patent  
10       Specification No. 2921070). It is readily prepared by  
reacting the corresponding acid with thionyl chloride or  
phosphorus trichloride. The acid is prepared according  
to the standard procedures for the manufacturing of flavones.

The condensation may be carried out in the presence or  
15       absence of a solvent. If carried out in the absence of a  
solvent, the reactants are heated together at a temperature  
of from 140°C to 200°C, and an excess of the 3-methyl-  
flavone-8-carboxylic acid is employed. If carried out in  
the presence of a solvent, the reactants are generally  
20       used in equimolar proportions, the temperature may be  
from 0°C to the reflux temperature of the solvent, and an  
acid-binding agent (hydrogen halide acceptor) may  
optionally be present. Suitable solvents include all inert  
inorganic solvents, particularly dimethylformamide, ethers  
25       and halogenated hydrocarbons. Aromatic hydrocarbons, such

as benzene and toluene, are also useful, especially when the reaction is carried out at reflux temperature. The acid-binding agent may be any of those customarily used in such condensations, for example, organic bases such as triethylamine and inorganic bases such as alkali metal hydroxides and alkali metal carbonates.

The invention also provides a further process for the preparation of the compounds having the general formula I in which Z represents a group of the general formula II wherein n is 1, R and R<sub>1</sub> both represent hydrogen atoms and R<sub>2</sub> represents a hydroxy group. This further process comprises reacting a compound of the general formula IV



wherein R<sub>3</sub> is as above defined with 2,3-epoxypropyl 3-methylflavone-8-carboxylate in the presence of a catalyst. The 2,3-epoxypropyl 3-methylflavone-8-carboxylate is a novel compound, but can be prepared by condensing a 3-methylflavone-8-carboxylic acid halide (preferably the chloride) with 2,3-epoxy-1-propanol. The reaction may be carried out in the presence of an organic solvent, such as any of those previously mentioned or a nitrile such as acetonitrile. The catalyst may be an organic base such as triethylamine.

Generally equimolar amounts of reactants are employed, and

the temperature ranges from 20 to 80°C. The reaction is preferably carried out at 40-60°C.

The salts according to the invention may be prepared from the basic esters obtained by the processes described above according to conventional methods such as addition of an acid to the free base dissolved in a suitable solvent. Suitable acids include hydrogen halides, phosphoric acid, nitric acid, alkylsulphonic acids, arylsulphonic acids, monofunctional and bifunctional carboxylic acids, hydroxy-  
-carboxylic acids and 1,5-naphthalenedisulphonic acid. Isolation and purification may be effected conventionally.

The invention additionally provides a pharmaceutical composition comprising a compound having the general formula I as above defined or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

The active compounds according to the invention exhibit a powerful smooth muscle relaxant and a calcium blocking action. They are also good anaesthetic and anti-inflammatory agents. As stated above, their stability at physiological pH is, however, the most interesting factor when compared with similar flavone derivatives.

The stability was studied at 37°C in gastric fluid simulated (U.S.P. XX, 1105, 1980) and in phosphate buffer (pH 7.4) by spectrodensitometric determination of 3-methylflavone-

-8-carboxylic acid resulting from eventual hydrolysis. As comparison substance 2-piperidino-ethyl 3-methylflavone-8-carboxylate hydrochloride (Flavoxate) was selected, this being the best of the esters disclosed in our United States Patent Specification No. 2,921,070.

The results are reported in Table I. In this Table, and in subsequent Tables, the numbers identifying the active compounds are those assigned to the respective active compounds in the Examples which follow and which describe their preparation.

TABLE I

Stability test, pH 7.4

<u>Active compound</u>		<u>1 hour</u>	<u>3 hours</u>
	1	100	100
15	2	100	100
	3	40	30
	4	68	34
	5	96	91
	6	100	100
20	7	44	25
	8	85	70
	9	88	87
	10	100	100
	11	100	100
25	12	100	100
	13	100	100
	FLAVOXATE	22	10



The LD<sub>50</sub> of the new esters was determined in mice both i.p. and per os, following the method described by C.S. Weil (Biometrics, 8, 249, 1952). The results obtained are reported in Table II.

5

TABLE II

	Active compound	LD <sub>50</sub>	mM/Kg
		i.p.	os
	1	0.56	1.86
	2	0.16	0.69
10	3	0.5	0.85
	7	0.58	3.10
	8	--	2.16
	9	0.19	1.08
	10	0.15	0.85
15	11	0.36	0.77
	12	0.42	0.95
	13	0.12	0.50
	FLAVOXATE	0.90	1.89

20

25

The calcium blocking activity was tested on guinea pig depolarized taenia coli, according to the method described by Ferrari and Carpenedo (Arch.Int.Pharmacodyn., 174, 223, 1968). The guinea pig taenia coli was allowed to stabilize in Tyrode solution without Ca<sup>++</sup>. It was then washed with K<sub>2</sub>SO<sub>4</sub> Ringer solution and afterwards perfused with KNO<sub>3</sub>

Ringer. Cumulative concentrations of  $\text{CaCl}_2$  were added to the organ bath in absence or presence of the drug to test. The obtained results are reported in Table III.

TABLE III

5 Calcium blocking activity

Active compound	ED <sub>50</sub> ( $\mu\text{M}$ )
1	24
2	16
3	19
10 5	8.6
6	7.5
8	7.3
9	26
FLAVOXATE	25

15

The antispastic activity was evaluated following the Magnus method (Pflügers Arch.Gen.Physiol., 102, 123, 1904). Two equal contractions were induced by  $\text{BaCl}_2$  at a concentration ranging between 1 and  $4 \cdot 10^{-4}$  M in guinea pig ileum maintained at  $30^\circ\text{C}$  in Ringer solution and aerated with Carbogen.

25 The drug to test was administered and, a minute later,  $\text{BaCl}_2$  to the same concentration. The inhibition of the contraction was observed. The results are given in Table IV.

TABLE IV

Active Compound	ED <sub>50</sub> (μM)
1	4
2	6.2
5 3	9.7
4	6.7
5	2.4
6	3.4
8	2.7
10 9	4
12	4.3
13	2.1
14	7.7
FLAVOXATE	5.6
15	

The smooth muscle relaxant activity of the novel flavone  
 derivatives has been also studied through the spontaneous  
 mobility of guinea pig isolated ureter. The test has  
 been executed according to the Trendelenburg method  
 (Arch.Exp.Path.Pharmak., 81, 55, 1917). The ureter was  
 allowed to stabilize in Tyrode solution with the upper  
 part closed and the inner part connected to a pressure  
 transducer. The drugs to test were given in a cumulative  
 way and the spontaneous circular and longitudinal

contractions of the ureter were measured. The results obtained are listed in Table V.

TABLE V

Antispastic activity Isolated ureter ( $ED_{50}, \mu M$ )

5	Active compound	circular contractions	longitudinal contractions
	1	8.5	6.9
	5	12	2.8
	6	5.3	2.5
	8	5	2.5
10	12	20	9

The following Examples illustrate the invention.

EXAMPLE 1

To a mixture consisting of 7.86 g of 3-(2-methylpiperidino)-  
-propanol, 40 ml of anhydrous dimethylformamide and 10.5  
15 g of anhydrous potassium carbonate, 14.9 g of 3-methyl-  
flavone-8-carboxylic acid chloride were added. The  
mixture was heated at 60°C for 8 hours under stirring then  
it was poured in 500 ml of icy water. The precipitate  
thus formed was extracted with diethyl ether, washed  
20 with water and dried. The solvent was evaporated off and  
the compound, as brown oil residue, was transformed into  
the corresponding hydrochloride (1) by adding hydrogen  
chloride in isopropanol. The 3-(2-methylpiperidino)-propyl  
3-methylflavone-8-carboxylate hydrochloride melts at  
25 185-187°C.

EXAMPLE 2

To a stirred suspension consisting of 5.75 g of 3-hydroxy-N-methylpiperidine and 10.4 g of anhydrous potassium carbonate in 50 ml dimethylformamide, 14.9 g of 3-methylflavone-8-carboxylic acid chloride were added. The mixture was stirred at ambient temperature for 20 hours, poured into icy water and the precipitate thus formed was extracted with ethyl acetate. The extract was neutralized with water and dried. The solvent was evaporated off and the residue was dissolved in isopropanol. After cooling, hydrogen chloride in isopropanol was added. The hydrochloride (11) was washed with diethyl ether and crystallized from isopropanol. The desired N-methyl-3-piperidyl 3-methylflavone-8-carboxylate hydrochloride melts at 228-229°C. The free base was crystallized from hexane, mp 90-93°C.

EXAMPLE 3

To a stirred mixture, cooled at 10-15°C, and consisting of 12.8 g of 3-hydroxyquinuclidine, 240 ml of dimethylformamide and 20 g of triethylamine, were added in 30-40 minutes 29.8 g of 3-methylflavone-8-carboxylic acid chloride. The temperature was allowed to reach 20-25°C, the mixture was stirred for 4 hours and then poured into icy water. The precipitate thus formed was separated, washed with water and then extracted with ethyl acetate. The extract was washed with aqueous sodium carbonate solution, then with water and dried. The residue was chromatographed on a

silica gel column using ethyl acetate : methanol (7:3 by volume) and chloroform : methanol (87:13 by volume) as eluent. 11.25 g of the desired compound, mp 180-181°C, were obtained. The free base was transformed into the  
5 corresponding hydrochloride (13) by adding hydrogen chloride in ethanol. The 3-quinuclidyl 3-methylflavone-8-carboxylate hydrochloride was crystallized from ethanol, mp 302-305°C.

#### EXAMPLE 4

10 To a solution of 4.6 g of cis-2-piperidino-cyclohexanol in 100 ml of anhydrous benzene, stirred and maintained at 20-25°C, 7.5 g of 3-methylflavone-8-carboxylic acid chloride were added over a period of 15 minutes. The mixture was refluxed for 18 hours, then cooled to ambient  
15 temperature. The product thus formed was filtered off, washed with ethyl acetate, dried, and crystallized from ethanol. The cis-2-piperidino-cyclohexyl 3-methylflavone-8-carboxylate hydrochloride (8) melts at 258-259°C. The trans form (14) was similarly obtained by starting  
20 from trans-2-piperidino-cyclohexanol. Its hydrochloride melts at 222-225°C. Using 1,1-dimethyl-2-piperidino-ethanol instead of cis-2-piperidino-cyclohexanol, 1,1-dimethyl-2-piperidino-ethyl 3-methylflavone-8-carboxylate was prepared. The compound was directly isolated as its  
25 hydrochloride (5) of melting point 203-207°C.

From this salt the free base was separated. It melted at 103-105°C. Moreover, the following salts have been prepared:

	Nitrate	mp. 179°C (with decomposition)
5	Sulphate	mp. 208°C (with decomposition)
	Phosphate	mp. 175-176°C (with decomposition)
	Maleate	mp. 144-148°C
	p-Toluenesulphonate	mp. 149-152°C

Using 1,1-dimethyl-2-(2-methylpiperidino)-ethanol  
10 instead of cis-2-piperidino-cyclohexanol, 1,1-dimethyl-  
-2-(2-methyl-piperidino)-ethyl 3-methylflavone-8-  
-carboxylate (6) was obtained. This compound, as  
hydrochloride, melts at 194-195°C.

The free base was separated from this salt, and had a  
15 melting point of 78-80°C. The following salts were  
also prepared:

	Hydrobromide	mp. 209°C
	Nitrate	mp. 170°C (with decomposition)
	Sulphate	mp. 184-188°C
20	Maleate	mp. 147-149°C
	p-Toluenesulphonate	mp. 157-159°C

EXAMPLE 5

5 A mixture comprising 8.9 g of tropine hydrochloride and  
22.5 g of 3-methylflavone-8-carboxylic acid chloride  
was heated for 4 hours at 170-175°C under a nitrogen  
atmosphere. When the reaction was over, a further 7.5 g  
of the flavone derivative were added and the mixture was  
10 heated again for 11 hours at the same temperature. After  
cooling, the product was powdered, suspended in water  
and stirred for 6 hours. The whole was filtered off and  
dilute sodium hydroxide solution was added to the  
solution. The precipitate was centrifuged, washed with  
15 water and dried. The desired compound, tropyl 3-methyl-  
flavone-8-carboxylate, was treated with hydrogen chloride  
in ethanol to give the corresponding hydrochloride (12),  
melting point 276-278°C.

EXAMPLE 6

20 21.3 g of 3-methylflavone-8-carboxylic acid chloride were  
slowly added, over a period of 4 hours at 20°C, to a  
stirred solution of 5.55 g of 2,3-epoxy-1-propanol and  
8.34 g of triethylamine in 165 ml of anhydrous benzene.  
The mixture was allowed to stand at 20-25°C for 20 hours,  
25 and then 60 ml of water were added. The whole was stirred  
for 15 minutes and the layers were separated. The organic



layer was washed and dried, the solvent was evaporated off and 18.95 g of 2,3-epoxypropyl 3-methylflavone-8-carboxylate, m.p. 103-105°C, was obtained.

5 A mixture comprising 16.8 g of the 2,3-epoxypropyl 3-methylflavone-8-carboxylate, 100 ml of acetonitrile, 5.5 ml of piperidine and 7 ml of triethylamine was heated at 60°C for 12 hours. The solvent was evaporated off and the brown, oily residue was washed twice with 75 ml of benzene. The 2-hydroxy-3-piperidino-propyl 3-methyl-  
10 flavone-8-carboxylate thus formed was converted into the corresponding hydrochloride (7) in the usual manner.  
Mp 187-189°C.

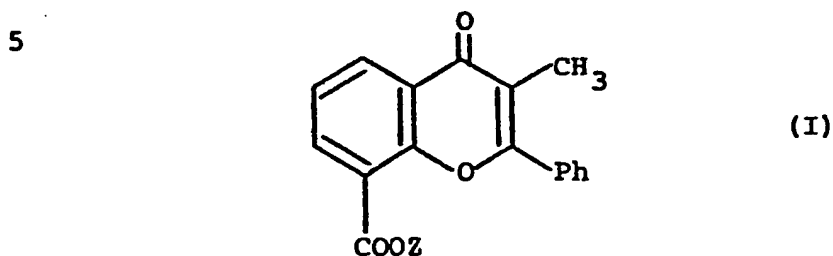
#### EXAMPLE 7

Following the procedure described in Example 2, the  
15 following esters of 3-methylflavone-8-carboxylic acid were prepared from appropriate starting materials:

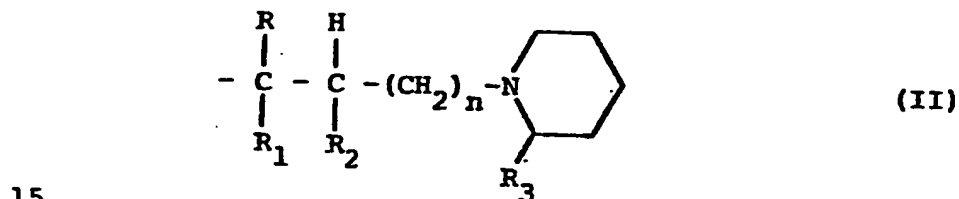
- (2) 1-methyl-3-piperidino-propyl, separated as its hydrochloride hemihydrate, mp 161-168°C;
- (10) 1-methyl-4-piperidyl, melting at 103-105°C;
- 20 (3) 1-methyl-2-piperidino-ethyl, separated as its hydrochloride hydrate, mp 218-220°C;
- (4) 1-phenyl-2-piperidino-ethyl (hydrochloride) of melting point 219-221°C; and
- (9) 2-piperidinomethyl cyclohexyl, as hydrochloride,  
25 mp 236-237°C.

CLAIMS:

1. A 3-methylflavone-8-carboxylic acid ester having the general formula I



- 10 wherein Z represents an N-methylpiperidyl, tropyl or quinuclidyl group or a group of the general formula II



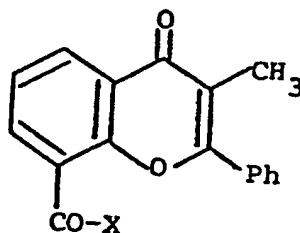
- 20 in which n is 0 or 1, R represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms or a phenyl group, R<sub>1</sub> represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, R<sub>2</sub> represents a hydrogen atom or a hydroxy group, or R, R<sub>1</sub> and R<sub>2</sub> together with the carbon atoms to which they are attached represent a cycloalkyl ring having from 4 to 6 carbon atoms, and R<sub>3</sub> represents a hydrogen atom or an alkyl group having from 1 to 4

carbon atoms; or a pharmaceutically acceptable salt of such an ester.

2. 3-(2-Methylpiperidino)-propyl 3-methylflavone-8-carboxylate.
- 5 3. N-Methyl-3-piperidyl 3-methylflavone-8-carboxylate.
4. 3-Quinuclidyl 3-methylflavone-8-carboxylate.
5. cis-2-Piperidino-cyclohexyl 3-methylflavone-8-carboxylate.
6. trans-2-Piperidino-cyclohexyl 3-methylflavone-8-carboxylate.
- 10 7. 1,1-Dimethyl-2-piperidino-ethyl 3-methylflavone-8-carboxylate.
8. 1,1-Dimethyl-2-(2-methylpiperidino)-ethyl 3-methylflavone-8-carboxylate.
- 15 9. Tropyl 3-methylflavone-8-carboxylate.
10. 2-Hydroxy-3-piperidinopropyl 3-methylflavone-8-carboxylate.
11. 1-Methyl-3-piperidino-propyl 3-methylflavone-8-carboxylate.
- 20 12. 1-Methyl-4-piperidyl 3-methylflavone-8-carboxylate.
13. 1-Methyl-2-piperidino-ethyl 3-methylflavone-8-carboxylate.
14. 1-Phenyl-2-piperidino-ethyl 3-methylflavone-8-carboxylate.
- 25 15. 2-Piperidinomethyl-cyclohexyl 3-methylflavone-8-carboxylate.

16. A process for the preparation of a compound according to claim 1, the process comprising condensing a 3-methylflavone-8-carboxylic acid halide having the general formula III

5



(III)

10

wherein X represents a halogen atom with an aminoalcohol of the general formula ZOH wherein Z is as above defined.

15

17. A process according to claim 16 in which X represents a chlorine atom.

18. A process according to claim 16 or claim 17 carried out by heating the aminoalcohol with an excess of the flavone derivative at from 140°C to 200°C in the absence of a solvent.

20

19. A process according to claim 16 or claim 17 carried out by reacting the aminoalcohol with an equimolar amount of the flavone derivative in the presence of a solvent at a temperature of from 0°C to

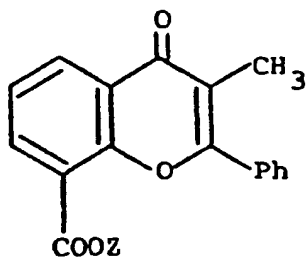
- 19 -

the reflux temperature of the solvent.

20. A process for the preparation of a compound according to claim 1, the process being substantially as described herein with reference to any of Examples 1 to 5 or 7.

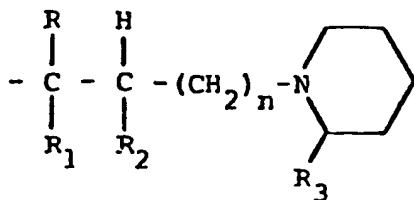
21. A process according to claim 19 carried out in the presence of an acid-binding agent.

22. A process for the preparation of a 3-methyl-flavone-8-carboxylic acid having the general formula I



(I)

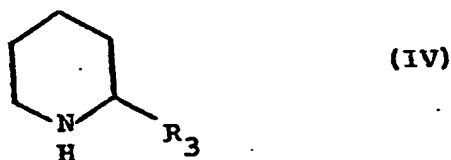
10 wherein Z represents a group of the general formula II



(II)

- 20 -

wherein  $\underline{n}$  is 1, R and  $R_1$  both represent hydrogen atoms,  $R_2$  represents a hydroxy group and  $R_3$  represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, the process comprising  
5 reacting a compound of the general formula IV



wherein  $R_3$  is as above defined with 2,3-epoxypropyl 3-methylflavone-8-carboxylate in the presence of a catalyst.

23. A process according to claim 22 in which the  
10 catalyst is triethylamine.

24. A process according to claim 23 carried out in a solvent at from 20°C to 80°C using equimolar proportions of the flavone and piperidine derivatives.

25. A process for the preparation of a 3-methyl-

- 21 -

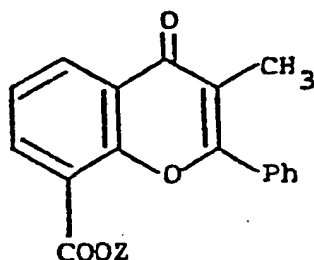
flavone-8-carboxylic acid having the general formula I as defined in claim 22, the process being substantially as described herein with reference to Example 6.

- 5      26. A pharmaceutical composition comprising a 3-methylflavone-8-carboxylic acid ester according to claim 1 or a pharmaceutically acceptable salt of such an ester in admixture with a pharmaceutically acceptable diluent or carrier.

CLAIMS:

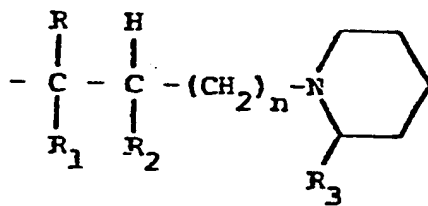
1. A 3-methylflavone-8-carboxylic acid ester having the general formula I

5



(I)

- 10 wherein Z represents an N-methylpiperidyl, troyyl or quinuclidyl group or a group of the general formula II



(II)

15

- in which  $n$  is 0 or 1, R represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms or a phenyl group,  $R_1$  represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms,  $R_2$  represents a hydrogen atom or a hydroxy group, or R,  $R_1$  and  $R_2$  together with the carbon atoms to which they are attached represent a cycloalkyl ring having from 4 to 6 carbon atoms, and  $R_3$  represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, with the proviso that R,  $R_1$ ,  $R_2$  and  $R_3$  do not all simultaneously represent hydrogen
- 20

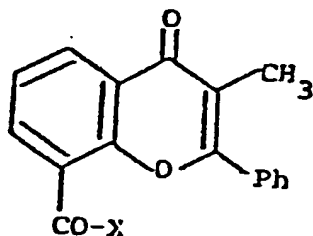


Amended  
claims

atoms; or a pharmaceutically acceptable salt  
of such an ester.

2. 3-(2-Methylpiperidino)-propyl 3-methylflavone-8-carboxylate.
- 5 3. N-Methyl-3-piperidyl 3-methylflavone-8-carboxylate.
4. 3-Quinuclidyl 3-methylflavone-8-carboxylate.
5. cis-2-Piperidino-cyclohexyl 3-methylflavone-8-carboxylate.
6. trans-2-Piperidino-cyclohexyl 3-methylflavone-8-
- 10 -carboxylate.
7. 1,1-Dimethyl-2-piperidino-ethyl 3-methylflavone-8-carboxylate.
8. 1,1-Dimethyl-2-(2-methylpiperidino)-ethyl 3-methylflavone-8-carboxylate.
- 15 9. Tropylyl 3-methylflavone-8-carboxylate.
10. 2-Hydroxy-3-piperidinopropyl 3-methylflavone-8-carboxylate.
11. 1-Methyl-3-piperidino-propyl 3-methylflavone-8-carboxylate.
- 20 12. 1-Methyl-4-piperidyl 3-methylflavone-8-carboxylate.
13. 1-Methyl-2-piperidino-ethyl 3-methylflavone-8-carboxylate.
14. 1-Phenyl-2-piperidino-ethyl 3-methylflavone-8-carboxylate.
- 25 15. 2-Piperidinomethyl-cyclohexyl 3-methylflavone-8-carboxylate.

16. A process for the preparation of a compound according to claim 1, the process comprising condensing a 3-methylflavone-8-carboxylic acid halide having the general formula III



(III)

wherein X represents a halogen atom with an aminoalcohol of the general formula ZO<sub>2</sub>H wherein Z is as defined in claim 1.

17. A process according to claim 16 in which X represents a chlorine atom.

18. A process according to claim 16 or claim 17 carried out by heating the aminoalcohol with an excess of the flavone derivative at from 140°C to 200°C in the absence of a solvent.

19. A process according to claim 16 or claim 17 carried out by reacting the aminoalcohol with an equimolar amount of the flavone derivative in the presence of a solvent at a temperature of from 0°C to

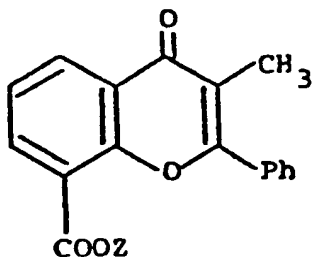
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- 19 - Amended  
Claims

the reflux temperature of the solvent.

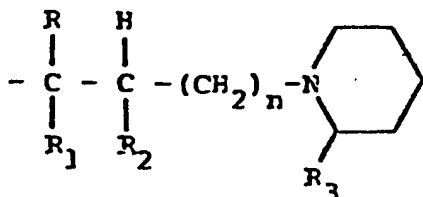
20. A process according to claim 19 carried out in the presence of an acid-binding agent.

21. A process for the preparation of a 3-methyl-  
5 -flavone-8-carboxylic acid having the general formula I



(I)

wherein Z represents a group of the general formula II

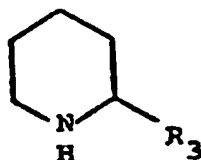


(II)

wherein n is 1, R and R<sub>1</sub> both represent hydrogen atoms, R<sub>2</sub> represents a hydroxy group and R<sub>3</sub> represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, the process comprising

Amended  
Claims

reacting a compound of the general formula IV



(IV)

wherein R<sub>3</sub> is as defined in claim 1 with  
2,3-epoxypropyl 3-methylflavone-8-carboxylate  
in the presence of a catalyst.

- 5        22. A process according to claim 21 in which the  
catalyst is triethylamine.
23. A process according to claim 22 carried out  
in a solvent at from 20°C to 80°C using equimolar  
proportions of the flavone and piperidine  
10       derivatives.
24. A pharmaceutical composition comprising a  
3-methylflavone-8-carboxylic acid ester according  
to claim 1 or a pharmaceutically acceptable  
salt of such an ester in admixture with a  
15       pharmaceutically acceptable diluent or carrier.



European Patent  
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# EUROPEAN SEARCH REPORT

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EP 82303634.8

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
D, A	US - A - 2 921 070 (DA RE) * Column 1, lines 1-53; column 2, lines 12-19 *	1, 16, 19, 21	C 07 D 405/02 C 07 D 451/02 C 07 D 453/02 A 61 K 31/35 A 61 K 31/445
A	US - A - 4 217 351 (DREN) * Abstract *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 3)
			C 07 D 405/00 C 07 D 451/00 C 07 D 453/00
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons
			&: member of the same patent family, corresponding document
X	The present search report has been drawn up for all claims		
Place of search		Date of completion of the search	Examiner
VIENNA		22-10-1982	BRUS